

REMARKS

This Amendment and Response is in response to the non-final Office Action mailed on January 27, 2011. Claims 12-26 are pending with claims 21-26 withdrawn from consideration as allegedly belonging to a non-elected invention. Claims 12-20 are rejected under 35 U.S.C. § 103(a) as being unpatentable. In response, Applicants have amended Claim 12, 15 and 17 to further distinguish the claimed invention from the cited references. Applicants submit that the amendments to the claims do not add any new matter. Last, Applicants would like to thank Examiner Wilder for the telephonic interview held on June 1, 2011 during which the cited art of record and a proposed claim amendment were discussed.

In the Office Action, Claims 12, 13, 14 and 18 are rejected under 35 U.S.C. 103(a) as being unpatentable over *Bao et al.* (U.S. Publication No. 2003/0129611) ("*Bao*") in view of *Yoshimoto et al.* (Chemical Communication, Issue 24, pages 2960-2961, October 2003) ("*Yoshimoto*"). In particular, the Examiner alleges that it would have been obvious to one of ordinary skill in the art at the time of the claimed invention to modify the method of *Bao* to encompass the use of a receptor having hydrogen bonding characteristics to detect the gene methods in the target nucleic acid, as taught by *Yoshimoto*, rather than the donor and acceptor molecular beacons which result in FRET as taught by *Bao* to alleviate some of the disadvantage of the FRET system and improve gene mutation detection (Office Action at pages 3-7). Applicants respectfully traverse this rejection for at least the reasons as set forth below.

To establish *prima facie* obviousness under 35 U.S.C. §103, all the claim limitations must be taught or suggested by the prior art. *In re Royka*, 490 F.2d 981, 180 USPQ 580 (CCPA 1974). This principle of U.S. law regarding obviousness was not altered by the recent Supreme Court holding in *KSR International Co. v. Teleflex Inc.*, 127 S.Ct. 1727, 82 USPQ2d 1385 (2007). In *KSR*, the Supreme Court stated that "Section 103 forbids issuance of a patent when 'the differences between the subject matter sought to be patented and the prior art are such the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains.'" *KSR Int'l Co. v. Teleflex Inc.*, 127 S.Ct. 1727, 1734, 82 USPQ2d 1385, 1391 (2007).

The question of obviousness is resolved on the basis of underlying factual determinations including (1) the scope and content of the prior art, (2) any differences between the claimed subject matter and the prior art, (3) the level of skill in the art. *Graham v. John Deere Co.*, 383

U.S. 1, 17-18, 148 USPQ 459, 467 (1966). See also *KSR*, 127 S.Ct. at 1734, 82 USPQ2d at 1391 (“While the sequence of these questions might be reordered in any particular case, the [Graham] factors continue to define the inquiry that controls.”) The Court in *Graham* noted that evidence of secondary considerations, such as commercial success, long felt but unsolved needs, failure of others, etc., “might be utilized to give light to the circumstances surrounding the origin of the subject matter sought to be patented.” 383 U.S. at 18, 148 USPQ at 467. Furthermore, the Court in *KSR* took the opportunity to reiterate a second long-standing principle of U.S. law: that a holding of obviousness requires the fact finder (here, the Examiner), to make explicit the analysis supporting a rejection under 35 U.S.C. 103, stating that “rejections on obviousness cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness. *Id.* at 1740-41, 82 USPQ2d at 1396 (citing *In re Kahn*, 441 F.3d 977, 988, 78 USPQ2d 1329, 1336 (Fed. Cir. 2006)). The Supreme Court in *KSR* stated that “a court *must* ask whether the improvement *is more than* the predictable use of prior art elements according to their established functions.” *KSR* at 1740 (emphasis added). As such, in addition to showing that all elements of a claim were known in the prior art and that one of skill had a reason to combine them, the Office must also provide evidence that a reasonable expectation of success existed. MPEP 2143.02.

While the *KSR* Court rejected a rigid application of the teaching, suggestion, or motivation (“TSM”) test in an obviousness inquiry, the Court acknowledged the importance of identifying “a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does” in an obviousness determination. *KSR*, 127 S. Ct. at 1731. The Court indicated that there is no necessary inconsistency between the idea underlying the TSM test and the *Graham* analysis.” *Id.* As long as the test is not applied as a “rigid and mandatory” formula, that test can provide “helpful insight” to an obviousness inquiry. *Id.* “Thus, in cases involving new compounds, it remains necessary to identify some reason that would have led a chemist to modify a known compound in a particular manner to establish prima facie obviousness of a new claimed compound.” *Takeda v. Alphapharm*.

The mere fact that prior art may be modified to produce the claimed product does not make the modification obvious unless the prior art suggests the desirability of the modification. *In re Fritch*, 23 U.S.P.Q.2d 1780 (Fed. Cir. 1992); *see, also, In re Papesh*, 315 F.2d 381, 137

U.S.P.Q. 43 (CCPA 1963). In addition, if the proposed modification or combination of the prior art would change the principle of operation of the prior art invention being modified, then the teachings of the references are not sufficient to render the claims *prima facie* obvious. *In re Ratti*, 270 F.2d 810, 123 USPQ 349 (CCPA 1959).

Prior to addressing the merits of this rejection, Applicants would like to clarify the teachings of *Bao* and correct a misinterpretation of *Bao* advanced by the Examiner in the Office Action. In particular, the Examiner states that "...SEQ ID NOS: 11 and SEQ ID NO: 12 represent the two single stranded nucleic acid complementary to the two partial sequences with the target base and SEQ ID NO: 10 representing the target sequence *having a mutation between SEQ ID NOS: 11 and 12.*" Emphasis added. Office Action at page 3. Applicants submit that SEQ ID NO: 11 and SEQ ID NO: 12 are probes, each linked to a donor or acceptor beacon, that anneal to a target strand (SEQ ID NO: 10) with the gap between the probes varied depending on the resonance energy transfer source used (*see, Bao* at paragraph [0040]). Upon probe hybridization to the target strand, a FRET signal is emitted (*see, Bao*, Figures 1-2, Example 1, and Table 1). Importantly, the target base in *Bao* is not exposed – but rather the target base is annealed to its complementary base in a probe sequence. Accordingly, the target base in *Bao* cannot reside within the gap between the probes.

Without acquiescing to the merits of the Examiner rejection, and solely to expedite prosecution of the instant application, Applicants have amended Claim 12 (from which Claims 13, 14 and 18 depend) to recite that a gap part is formed at a position directly opposed to a target base. Applicant submits that *Bao* or *Yoshimoto*, taken singly or in combination, fail to teach or suggest forming a gap part at a position directly opposed to a target base with two single-stranded detecting nucleic acids. Instead, *Bao* anneals two probes (detecting strands), each linked to a detectable molecular probe, to a target strand, where one of the probes is designed to anneal a specified mutated sequence (*see, Bao*, Example 1, Table 1). Notably, when both probes are annealed to the target strand – the gap between the strands is used to affect the strength of a detectable FRET signal. Notably, in *Bao*, the target base (*i.e.*, mutated position) does not reside in the gap part but rather anneals to a complementary base in one of the probes. As such, the target base in *Bao* is not exposed as in the instant application. Additionally, *Yoshimoto* merely provides a hydrogen-bonding ligand for nucleotide recognition. *Bao* and *Yoshimoto* are completely silent with respect to forming a gap part directly opposed to a target base with two

detecting strands. Given that *Bao* and *Yoshimoto* fail to teach or suggest each and every element of the claimed invention, they cannot obviate the instant claims.

Additionally, Applicants submit that *Bao* and *Yoshimoto* are not combinable because the proposed modification of *Bao* would render *Bao* inoperable for its intended purpose. The Examiner states “[i]t would have been prima facie obvious for one of ordinary skill in the art at the time of the claimed invention to have been motivated to modify the method of *Bao* to encompass the use of a receptor having hydrogen bonding characteristics to detect the gene mutation in the target nucleic acid rather than the donor and acceptor molecular beacons which result in FRET as taught by *Bao*...” Emphasis added; Office Action at page 5. Applicants submit that MPEP 2143.01 provides “[i]f a proposed modification would render the prior art invention being modified unsatisfactory for its intended purpose, then there is no suggestion or motivation to make the proposed modification. *In re Gordon*, 733 F.2d 900, 221 USPQ 1125 (Fed. Cir. 1984).” Moreover, MPEP 2143.01 states “[i]f the proposed modification or combination of the prior art would change the principle of operation of the prior art invention being modified, then the teachings of the references are not sufficient to render the claims *prima facie* obvious. *In re Ratti*, 270 F.2d 810, 123 USPQ 349 (CCPA 1959).” Applicants submit that the proposed modification of *Bao* (to use the receptor of *Yoshimoto* to detect a mutation) would render *Bao* inoperable for its intended purpose because the probe (detecting strand) of *Bao* that hybridizes to the target base (*i.e.*, mutated position) on the target strand could not be used if one of skill in the art was to use a receptor as disclosed in *Yoshimoto* to hybridize to and detect the target base. In other words, the modification of *Bao* advanced by the Examiner would mean that one of the probes of *Bao* could not be used since the probe is required by *Bao* to hybridize to the same target base to which the receptor of *Yoshimoto* would anneal. As such, *Bao* could not be used for its intended purpose as two probes could not be used to generate a detectable FRET signal. Thus, the modification of *Bao* as suggested by the Examiner renders *Bao* inoperable for its intended purpose.

Accordingly, for the above-mentioned reasons, Applicants respectfully request that the rejection of claims 12, 13, 14 and 18 under 35 U.S.C. 103(a) be reconsidered and withdrawn.

Additionally, Claims 15-17 and 19-20 are rejected under 35 U.S.C. 103(a) as being unpatentable over *Bao* in view of *Yoshimoto* as applied to claims 12-14 and 18 above, and further in view of Nakatani *et al.* (*J. American Chemical Society* (2001) 123: 12650-12657)

("Nakatani"). In particular, the Examiner alleges that it would have been obvious to one of ordinary skill in the art at the time the invention was made to practice the method of *Nakatani* in the method of *Bao* and *Yoshimoto* to fix any of the components, either the receptor or the one detecting nucleic acid to a substrate to form the sensor and then add the remaining components required to form the double-stranded hybrid (Office Action at pages 7-11). Applicants respectfully traverse this rejection for at least the reasons articulated in the 35 U.S.C. 103(a) rejection discussed above.

For the foregoing reasons, Applicants respectfully request reconsideration of the above-identified patent application and earnestly solicit an early allowance of same. In the event there remains any impediment to allowance of the claims which could be clarified in a telephonic interview, the Examiner is respectfully requested to initiate such an interview with the undersigned.

Respectfully submitted,
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